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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/813,331	03/29/2004	Bill J. Peck	10031531-1	5115

22878 7590 02/05/2009

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EXAMINER	
WILDER, CYNTHIA B	

ART UNIT	PAPER NUMBER
1637	

NOTIFICATION DATE	DELIVERY MODE
02/05/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

IPOPS.LEGAL@agilent.com

Office Action Summary	Application No.	Applicant(s)	
	10/813,331	PECK ET AL.	
	Examiner	Art Unit	
	CYNTHIA B. WILDER	1637	

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 November 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4-8 and 10-28* is/are pending in the application.

4a) Of the above claim(s) *17-27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-8,10-16 and 28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *29 March 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 11/19/2008 has been entered. Claims 1, 10 and 11 have been amended. Claims 3, 9 and 25 have been canceled. Claims 1-2, 4-8, 10-24, 26-28 are pending. Claims 17-24, 26, and 27 are withdrawn from consideration as being drawn to a non-elected invention. Claims 1, 2, 4-16 and 28 are addressed in this Office action. All of the arguments have been thoroughly reviewed and considered but are deemed moot in view of the new ground(s) of rejections necessitated by Applicant's amendment of the claims.

Previous Rejections

2. The prior art rejections under 35 USC 102(b) are withdrawn in view of Applicant's amendment of the claims. The claim rejections under 35 USC 103(a) are withdrawn in view of Applicant's amendment.

New Ground(s) of the Rejections

THE NEW GROUND(S) OF REJECTIONS WERE NECESSITATED BY APPLICANT'S AMENDMENT OF THE CLAIMS:

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

5. Claim 1, 2, 4-8, 10-16 and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Perbost (US 6900048, effective filing date in view of Anderson et al (citation made of record in prior Office actions).

Regarding claim 1, Perbost teaches a method of producing an addressable array of at least two different nucleic acid ligands covalently bonded to a surface of a substrate (Abstract), said method comprising: (a) contacting blocked nucleoside monomers to at least a first location and a second location of a substrate surface displaying functional groups under conditions sufficient for said blocked nucleoside monomers to covalently bond to said surface in said first and second locations to

produce a substrate surface displaying covalently bound blocked monomers; (b) contacting said surface displaying blocked nucleoside monomers with an oxidation fluid to produce an oxidized surface; (c) contacting said oxidized surface with a deblocking fluid {deprotecting fluid}; (d) removing deblocking fluid from said deblocked surface by displacing said deblocking fluid from said surface with a wash fluid; and (e) reiterating steps (a) to (d) at least once to produce said addressable array having a first polymeric ligand at said first location of said substrate and a second polymeric ligand at said second location of said substrate (col. 10, lines 26-65).

Perbost specifically teaches the sequential steps of moving the substrate to a flow cell (flood station # 68) for oxidation, capping and washing steps over the entire substrate (col. 10, lines 48-50). Thus during a single step, the substrate is exposed to multiple fluids while at the flood station and therefore sequential addition of a plurality of liquids absent a drying steps.

Perbost does not discuss wherein the sequential application of liquids comprises flowing the fluids in a manner sufficient to produce a stratified fluid interface that moves across the surface.

However, sequential application of liquids via stratified liquid-liquid displacement was well-known and routinely practiced in the art of polymer synthesis at the time the claimed invention was made as taught by Anderson et al.

Anderson et al disclose a similar method comprising contacting a blocked monomer at first and second locations having functional groups (e.g. cpg supports

having the first monomer attached, Column 19, lines 55-58) under conditions sufficient for the monomer to covalently bond to the surface. Anderson et al further teach detritylation of the nucleotide with a blocking fluid; namely, step (i) of Table I (column 20), which generates an unblocked attached nucleoside nucleotide. Anderson et al further teach displacing the deblocking fluid with a purging fluid; namely, the solid supports are exposed to reagents sequentially wherein the reagents are kept separate based on density (column 5, lines 3-38 and column 6, lines 13-36) forming a liquid-liquid interface such that the solid support is not exposed to a triple phase interface (column 12, lines 28-67 and Fig. 2A-2D). Anderson et al also teach the reacting of the unblocked attached nucleotide with another blocked nucleoside monomer; namely, coupling step ii of Table I (column 20); removing blocking groups to generate a function group and reiterating the steps to produce the array of at least two ligands (Column 19, line 55-Column 20, line 50). Anderson et al teach wherein the solid supports of the array are exposed to reagents sequentially wherein the reagents are kept separate based on density (Column 5, lines 3-38 and Column 6, lines 13-36) forming a liquid-liquid interface such that the solid support is not exposed to a triple phase interface (Column 12, lines 28-67 and Fig. 2A-2D). Anderson et al further disclose wherein displacing comprises flowing the subsequent liquid across the surface to produce a stratified liquid interface that moves across the surface (Column 12, lines 28-67 and Fig. 2A-2D)

Anderson et al further teach the method wherein the sequentially applied liquids have a different density greater than zero (i.e. increasing density, Column 6, line 57-

Column 7, line 14) wherein the sequential contact is performed by displacing a previous liquid with an immediately subsequent liquid produce a stratified liquid interface that moves across the surface (Column 7, line 60-Column 8, line 3, Column 12, lines 28-67 and Fig. 2A-2D).

Anderson et al also teaches that reagent solutions used for polymer synthesis are incompatible (Column 3). To overcome the problems of incompatible reagents, Anderson introduces the reagents at differing densities so as to form a stratified liquid interface moving across the flow cell (Column 5, lines 1-19) thereby eliminating extensive washing between synthesis steps and reducing the waste of expensive reagents (Column 3, lines 54-59).

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to apply the fluid displacement synthesis method comprising flowing fluid in a manner sufficient to produce a stratified fluid interface of Anderson et al to the polymer synthesis method of Perbost. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success based on the problems using incompatible reagents as taught by Anderson et al (Column 3, lines 54-59) and for the benefit of eliminating the intervening washing thereby reducing waste of time and expensive reagents. One of ordinary skill would have been further motivated to apply the sequential application of synthesis reagents using displacing fluids of differing densities as taught by Anderson to the method of Perbost so as to maintain separation between incompatible reagents with precise control and timing (Anderson, Column 5, lines 1-38).

With respect to claim 2, Anderson et al disclose the method wherein the sequentially applied liquids have a different density greater than zero (i.e. increasing density, Column 6, line 57-Column 7, line 14).

With respect to claim 4, Anderson et al wherein the washing fluid has a density that is lower than the density of the deblocking fluid (Column 5, lines 3-38 and Column 6, lines 13-36). In one embodiment, Anderson et al teach the deblocking (detritylation) fluid has a density that is greater than that of methylene chloride (i.e., 1.325 g/mL; column 21, lines 1-10). Detritylation is followed with a wash using acetonitrile, which has a density of 0.714 g/mL (Table II, step 3). Calculating the density difference using pure methyl chloride results in an Atwood number of 0.2996; a higher density deblocking fluid gives a higher Atwood number.

With respect to claim 5, Anderson et al disclose wherein the wash is a low viscosity (see col. 7, lines 68 to col. 8, line 1 and Table II, step 3 with discloses that the wash solution is acetonitrile).

With respect to claims 6 and 8, Anderson et al discloses wherein the wash fluid is acetronitrile (column 13, line 67-column 14, line 1), which has a low viscosity (col. 7, line 68 to col. 8, line 1). It is commonly known in the art base standard physical data that acetonitrile has a viscosity of 0.38 cp. Therefore, it is an inherent property that the wash fluid (acetonitrile) has a viscosity that does not exceed about 1.2 cP.

With respect to claim 7, Anderson et al disclose wherein said wash fluid is an organic fluid (Table II, step 3).

With respect to claim 10, Perbost teaches wherein the fluid is flowed across said surface at a rate ranging from 0.1 to 1000 pL, usually 0.5 to 500 pL and more usually about 1.0 to 250 pL. Perbost teaches that a typical velocity at which the fluid is expelled from the chamber is more than about 1m/s, usually more than about 10 m/s and may be as great as about 20m/s or greater (col. 9, lines 17-23).

With respect to claim 11, Anderson et al teach wherein the method comprises a sensing movement (rotation) that moves a stratified interface across the surface (column 12, lines 28-67 and Fig. 2A-2D).

With respect to claim 12-14, Perbost teaches wherein the steps are performed in the same flow cell (Flood station #68) (col. 10, lines 26-65). Anderson et al also disclose the method wherein the steps are preformed in a flow cell i.e. internal space for fluid flow so as to contact solid support (Column 5, lines 20-38).

With respect to claim 15, Anderson et al disclose the method wherein said surface is contacted with a capping liquid prior to said deblocking (Column 13, line 59-Column 14, line 11 and Column 19, line 55-Column 20, line 50).

The claims 2 and 4-8, 10-15 merely recite a plethora of manipulation reagents and methodologies, as well as routine optimization or reaction components, concentrations, and parameters. Clearly such conventional and trivial modification and optimizations do not contribute towards patentability. Thus, one of ordinary skill in the art would have been motivated to modify the method of Perbost with the reagents of Anderson in the manner of the claims to achieve the expected benefits, optimizations an/or expanded applications. It would have been *prima facie* obvious to one of ordinary

skill in the art at the time of the invention to carry out the claimed methods with a reasonable expectation of success.

Regarding claim 16, Perbost teaches wherein the blocked nucleoside monomers are contacted with said surface by pulse-jet deposition (print head #210) (see col. 9, lines 11-30 and col. 10, lines , lines 26-65).

Regarding claim 28, Perbost et al teach wherein the substrate is planar (col 12, lines 50-55).

6. Claims 1, 2, 4-8, 10-16 and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bass as previously applied above in view of Anderson et al as previously applied in the previous Office action.

Regarding claims 1, 16 and 28, Bass et al teach a method of producing an addressable array of at least two different nucleic acid ligands covalently bonded to a surface of a substrate, said method comprising contacting blocked nucleoside monomers to at least a first location and a second location of a substrate surface displaying functional groups under conditions sufficient for said .blocked nucleoside monomers to covalently bond to said surface in said first and second locations to produce a substrate surface displaying covalently bound blocked monomers; (b) contacting said surface displaying blocked nucleoside monomers with an oxidation fluid to produce an oxidized surface; (c) contacting said oxidized surface with a deblocking fluid; (d) removing deblocking fluid from said deblocked surface by displacing said deblocking fluid from said surface with a wash fluid; and (e) reiterating steps (a) to (d) at

least once to produce said addressable array having a first polymeric ligand at said first location of said substrate and a second polymeric ligand at said second location of said substrate (col. 1. line 55 to col. 2, lines 1-9 and 28-34 and Figures 1-3, which is identical to the Figures 1-3 of the instant invention).

Bass does not provide any additional information on the wash fluid or deblocking fluid or wherein the method utilizes a flow cell. Bass also does not discuss wherein the displacing comprising flowing said wash fluid across said surface in a manner sufficient to produce a stratified fluid interface that moves across said surface.

Anderson et al disclose the method similar to that of Bass comprising contacting a blocked monomer at first and second locations having functional groups (e.g. cpg supports having the first monomer attached, Column 19, lines 55-58) under conditions sufficient for the monomer to covalently bond to the surface. Anderson et al further teach detritylation of the nucleotide with a blocking fluid; namely, step (i) of Table I (column 20), which generates an unblocked attached nucleoside nucleotide. Anderson et al further teach displacing the deblocking fluid with a purging fluid; namely, the solid supports are exposed to reagents sequentially wherein the reagents are kept separate based on density (column 5, lines 3-38 and column 6, lines 13-36) forming a liquid-liquid interface such that the solid support is not exposed to a triple phase interface (column 12, lines 28-67 and Fig. 2A-2D). Anderson et al also teach the reacting of the unblocked attached nucleotide with another blocked nucleoside monomer; namely, coupling step ii of Table I (column 20); removing blocking groups to generate a function group and reiterating the steps to produce the array of at least two ligands (column 19,

line 55-Column 20, line 50). Anderson et al further teach the method wherein the solid supports are exposed to reagents sequentially wherein the reagents are kept separate based on density (Column 5, lines 3-38 and Column 6, lines 13-36) forming a liquid-liquid interface such that the solid support is not exposed to a triple phase interface (Column 12, lines 28-67 and Fig. 2A-2D). Anderson et al disclose the method wherein displacing comprises flowing the subsequent liquid across the surface to produce a stratified liquid interface that moves across the surface (column 12, lines 28-67 and Fig. 2A-2D).

Anderson et al also teaches that reagent solutions used for polymer synthesis are incompatible (Column 3). To overcome the problems of incompatible reagents, Anderson introduces the reagents at differing densities so as to form a stratified liquid interface moving across the flow cell (Column 5, lines 1-19), thereby eliminating extensive washing between synthesis steps and reducing the waste of expensive reagents (Column 3, lines 54-59).

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to apply the fluid displacement synthesis of Anderson et al to the polymer synthesis of Bass et al. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success based on the problems using incompatible reagents as taught by Anderson et al (Column 3, lines 54-59) and for the benefit of eliminating the intervening washing thereby reducing waste of time and expensive reagents. One of ordinary skill would have been further motivated to apply the sequential application of synthesis reagents using displacing fluids of differing

densities as taught by Anderson to the method of Bass so as to maintain separation between incompatible reagents with precise control and timing (Anderson, Column 5, lines 1-38).

With respect to claim 2, Anderson et al disclose the method wherein the sequentially applied liquids have a different density greater than zero (i.e. increasing density, Column 6, line 57-Column 7, line 14).

With respect to claim 4, Anderson et al wherein the washing fluid has a density that is lower than the density of the deblocking fluid (Column 5, lines 3-38 and Column 6, lines 13-36). In one embodiment, Anderson et al teach the deblocking (detritylation) fluid has a density that is greater than that of methylene chloride (i.e., 1.325 g/mL; column 21, lines 1-10). Detritylation is followed with a wash using acetonitrile, which has a density of 0.714 g/mL (Table II, step 3). Calculating the density difference using pure methyl chloride results in an Atwood number of 0.2996; a higher density deblocking fluid gives a higher Atwood number.

With respect to claim 5, Anderson et al disclose wherein the wash is a low viscosity (see col. 7, lines 68 to col. 8, line 1 and Table II, step 3 with discloses that the wash solution is acetonitrile).

With respect to claims 6 and 8, Anderson et al discloses wherein the wash fluid is acetronitrile (column 13, line 67-column 14, line 1), which has a low viscosity (col. 7, line 68 to col. 8, line 1). It is commonly known in the art base standard physical data that acetonitrile has a viscosity of 0.38 cp. Therefore, it is an inherent property that the wash fluid (acetonitrile) has a viscosity that does not exceed about 1.2 cP.

With respect to claim 7, Anderson et al disclose wherein said wash fluid is an organic fluid (Table II, step 3).

With respect to claim 10, Anderson et al disclose a method of producing an array of at least two different polymeric ligands (e.g. oligonucleotides synthesized on control pore glass, the two different sequences being e.g. product and failed sequences, Column 20, lines 10-25) as previously discussed above. Anderson et al further teach the method wherein the steps are performed in a flow cell wherein the flow rate is controlled and monitored during passage of reagents (Column 5,lines 25-27; Column 14, lines 44-53 21). Anderson et al teach that it is important to control the flow rate because some synthesis steps take more or less time than other steps and because reagent waste resulting from excess use of reagents is expensive (Column 21, lines 30-65) but they are silent regarding specific flow rates. However, the reference clearly suggests that the flow rate is adjusted to maximize reagents and synthetic step. Therefore, It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to adjust the flow rate during the synthesis steps of Anderson to obtain optimal flow rates (e.g. about 1-20 cm/x). One of ordinary skill in the art would have been motivated to adjust the flow rate so as to maximize syntheses reaction with minimal waste of reagents as desired by Anderson et al (Column 21, lines 30-65).

With respect to claim 11, Anderson et al teach wherein the method comprises a sensing movement (rotation) that moves a stratified interface across the surface (column 12, lines 28-67 and Fig. 2A-2D).

With respect to claim 12-14, Anderson et al disclose the method wherein the steps are preformed in a flow cell i.e. internal space for fluid flow so as to contact solid support (Column 5, lines 20-38).

With respect to claim 15, Anderson et al disclose the method wherein said surface is contacted with a capping liquid prior to said deblocking (Column 13, line 59-Column 14, line 11 and Column 19, line 55-Column 20, line 50).

The claims 2 and 4-8, 10-15 merely recite a plethora of manipulation reagents and methodologies, as well as routine optimization or reaction components, concentrations, and parameters. Clearly such conventional and trivial modification and optimizations do not contribute towards patentability. Thus, one of ordinary skill in the art would have been motivated to modify the method of Bass et al with the reagents of Anderson in the manner of the claims to achieve the expected benefits, optimizations an/or expanded applications. It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to carry out the claimed methods with a reasonable expectation of success.

Response to Arguments

7. Applicant traverses the rejection on the following grounds: Applicant states that Bass and Anderson teach very different protocols and there is no teaching or suggestion to modify Bass in order to arrive at the rejected claims. Applicant teaches the methods of Bass and Anderson are very different. Applicant states as such, there can be no teaching or suggestion as to how one might modify Bass's *in situ* fabrication method to accommodate Anderson's teaching of fluid displacement in a rotating reactor.

Applicant states without the hindsight provided by the Applicants, one of skilled in the art would not have combined the cited art to arrive at removing deblocking fluid by flowing said wash fluid in a manner sufficient to produce a stratified fluid interface that moves across said surface. Applicant states that a careful consideration of the field of array synthesis reveals that the much of the teaching around the priority date of the instant application comprises drying steps in between wash steps and is completely devoid of the element of removing deblocking fluid from said deblocked surface by flowing said wash fluid across said surface in a manner sufficient to produce a stratified fluid interface that moves across said surface. Applicant cites several patents and stats that the prevalent teachings in the art of array synthesis employ air drying and are completely silent on removing deblocking fluids from said deblocked surfaced. Applicant states that Anderson is completely silent on sensing movement of the stratified fluid interface.. Applicant further contends that Anderson's rotating rotor cannot be a flow cell based on functional embodiment of the rejected claims construed by one of skilled in the art. Applicant states an addressable array cannot be mounted or placed in a rotating rotor Applicant states that neither Bass nor Anderson can teach the element of a "flow cell". Applicant states that not only is there no teaching or suggestion to combine the references in the manner suggested by the Examiner, the combination of the references would also result in a change of the principle of operation or render them inoperable. Applicant states that an addressable array cannot exist in suspension nor can deposition at discrete location on an array be operable if the substrate were to be enclosed in Anderson's rotor. Applicant concludes that the

proposed modification to modify Bass or Anderson to comport with the rejected claims would either change the principle of operation or render the methods taught inoperable.

8. All of applicant's arguments have been thoroughly reviewed and considered but are not found persuasive for the reasons that follow: In response to Applicant arguments that the combination of Bass et al in view of Anderson would not result in the instant invention without hindsight reasoning, it is noted that In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). In this case, both Bass and Anderson teach methods of oligonucleotide synthesis via monomer addition using the same reagents, Anderson et al further teaches that reagents solutions used for polymer synthesis are incompatible (column 3). To overcome the problems of incompatible reagents, Anderson introduces the reagents at differing densities so as to form a stratified liquid interface moving across the flow cell (col. 5, lines 1-19), thereby eliminating extensive washing between synthesis steps and reducing the waste of expensive reagents (col. 3, lines 54-59). It is thus maintained that Anderson teaches oligonucleotide synthesis via applications of stratified reagents and it is maintained that Anderson provides sufficient

reasoning and motivation for using the stratified reagents in the method of Bass.

In response to Applicant's arguments that the combination of Bass et al in view of Anderson would result in an inoperable method because Anderson uses a rotor and introduce the reagents during rotation, it is noted that Applicant provides no evidence to support this conclusion. MPEP states that "The arguments of counsel cannot take the place of evidence in the record. In re Schulze, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965). Examples of attorney statements which are not evidence and which must be supported by an appropriate affidavit or declaration include statements regarding unexpected results, commercial success, solution of a long-felt need, inoperability of the prior art, invention before the date of the reference, and allegations that the author(s) of the prior art derived the disclosed subject matter from the applicant". (see (MPEP 716.01(c). Additionally it is noted that the teachings of Anderson is not limited only to synthesis within a rotor because Anderson also applicable to a "column at rest" (see col. 5 and abstract). Thus, Anderson provides an "optional" method capable of being used for oligonucleotide synthesis. Additionally, the primary reference of Bass is specifically interested in applying multiple and sequential reagents during the in situ synthesis steps using the flood station (col. 9, lines 1-9). Bass further teaches wherein a single flood station is used for adding multiple and sequential reagents. This clearly supports the concept of displacing one fluid for another fluid on the surface of a substrate. Anderson teaches sequential reagents addition and teaches the advantages of doing so. Accordingly, the Examiner maintains that the combination of

Bass et al in view of Anderson meets the limitations of the instant invention as currently claimed.

In response to applicant's argument that Bass et al in view of Anderson is nonanalogous art, it has been held that a prior art reference must either be in the field of applicant's endeavor or, if not, then be reasonably pertinent to the particular problem with which the applicant was concerned, in order to be relied upon as a basis for rejection of the claimed invention. See *In re Oetiker*, 977 F.2d 1443, 24 USPQ2d 1443 (Fed. Cir. 1992). In this case, both Bass et al and Anderson are both interested in synthesizing a plurality of oligonucleotides via monomer phosphoramidite chemistry. It would have been obvious to the ordinary artisan to apply the advantageous elements of Anderson to the synthesis method of Bass based on the explicit need and advantages taught by Anderson i.e., to overcome the problems of incompatible reagents, by introducing reagents at differing densities so as to form a stratified liquid interface moving across the flow cell (col. 5, lines 1-19) thereby eliminating extensive washing between synthesis steps and reducing the waste of expensive reagents (col. 3, lines 54-59). Applicant's arguments are not found persuasive. Accordingly, the rejections are maintained.

Conclusion

9. No claims are allowed. Any inquiry concerning this communication or earlier communications from the examiner should be directed to CYNTHIA B. WILDER whose telephone number is (571)272-0791. The examiner can normally be reached on a flexible schedule.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

1/30/2009

/Cynthia B. Wilder/

Examiner, Art Unit 1637